REMARKS/ARGUMENTS

Claims 57-84 were pending in the instant application.

Claims 62 and 73-79 were withdrawn from consideration as being drawn to a non-elected invention.

Accordingly, claims 57-61, 63-72, and 80-84 were pending and under examination in the instant application.

I. Amendments to the Claims:

Claims 63, 65, 70, 72, and 84 have been amended herewith. Support for the amendments can be found throughout the application as filed. Accordingly, no new matter has been added by way of the instant amendment to the claims.

II. Election/Restrictions:

Applicants gratefully note that the Examiner, after reconsideration, has decided to withdraw the species election requirement of January 10, 2007 (*see*, Office Action, page 2).

III. Information Disclosure Statement:

Attached as **Appendix A** is a Supplemental Information Disclosure Statement for the instant application.

IV. Rejections Under 35 U.S.C. § 112, Second Paragraph:

(a) Claims 65, 72, and 84 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite with respect to the recitation of the concentration in these claims (*see*, Office Action, page 3).

Claims 65, 72, and 84 have been amended herewith to recite, in relevant part, that the concentration of microplasmin is per eye. That the disclosed amounts are per eye is believed to be clear to a person skilled in the art based upon the specification. Upon entry of the instant

amendment to the claims, Applicants respectfully aver that the grounds for this rejection have been overcome.

(b) Claims 63 and 70 were rejected under 35 U.S.C. § 112, second paragraph, for purportedly being unclear in reciting that the method is performed in the absence of vitrectomy (*see*, Office Action, page 3).

Claims 63 and 70 have been amended as requested by the Examiner to specify that the method is performed in the absence of non-pharmacological vitrectomy (*i.e.*, surgical vitrectomy). As noted by the Examiner, it would be clear based upon the instant specification that "non-pharmacological vitrectomy" is what is referenced in the claims and specification. In view of the instant amendment to the claims, Applicants respectfully submit that the grounds for this rejection have been overcome.

V. **Rejections Under 35 U.S.C. § 103(a):**

(a) Claims 57-61, 63-72, and 80-84 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Trese *et al.* (U.S. Patent No. 5,304,118) in view of Collen *et al.* (WO 2002/50290) in further view of Wu *et al.* (U.S. Patent No. 4,774,087) (*see*, Office Action, page 4).

The Office Action relies on Trese for allegedly teaching a method of inducing posterior vitreous detachment in a human eye and treating certain diseases and dysfunctions in the eye by injecting one to three units of plasmin during vitrectomy. The Office Action also alleges that Trese teaches that these methods can be used before or simultaneously with surgical vitrectomy. The Office Action relies on Collen for teaching recombinant mammalian plasminogen derivatives and stabilization of such recombinant proteins. Finally, the Office Action relies on Wu to purportedly provide motivation to use microplasmin over plasmin.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), the Examiner must show "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the new invention does . . . ." *KSR International Col. V. Teleflex, Inc.*, 127 S. Ct. 1727, 1731 (2007). In addition, the Federal Circuit in *Takeda Chemical Industries, Ltd. et al. v. Alphapharm Pty., Ltd et al.*, Fed. Cir. 06-1329 (June 28, 2007) articulated the

standards concerning *prima facie* obviousness of structurally similar compounds. As stated by the Federal Circuit, "in order to find a *prima facie* case of unpatentability [of structurally similar compounds], a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required." *Takeda* at 9. Thus, without an objective teaching, suggestion, or motivation in the applied prior art taken as a whole and knowledge generally available to one of ordinary skill in the art that would have led that person to the claimed invention as a whole including each and every limitation of the claims there is no *prima facie* case of obviousness.

Applicants respectfully aver that there is no motivation to combine Trese with Collen and/or Wu without recourse to the teaching in Applicants' disclosure.

As a preliminary matter, Applicants note that Trese relates to methods for performing a vitrectomy on an eye, whereas Collen and Wu (when given a most expansive reading) relate to treatment of focal cerebral ischemic infarctions. There is simply no teaching or suggestion in Collen or Wu that microplasmin may be used to: liquefy the vitreous, induce posterior vitreous detachment, treat vitreoretinal diseases or disorders, or be used in a method of performing a non-pharmacological vitrectomy. The mere fact that microplasmin has been described in Collen and Wu for use in treatment of strokes does not render obvious its use in the eye for treatment as claimed.

As set forth in detail below, there are significant structural differences between plasmin and microplasmin. There are also significant differences between the methods for liquefying the vitreous, inducing posterior vitreous detachment, treating vitreoretinal diseases or disorders and performing a non-pharmacological vitrectomy as claimed, and the treatment of strokes as disclosed in Collen and Wu. There is nothing cited to suggest any similarities in the mechanisms of action and thus treatment of these diseases. The methods of administration and effective doses also would be different, for example. Furthermore, the use of plasmin in the eye by Trese does not in any way suggest that microplasmin would be useful for related purposes for the reasons discussed further below. As such, there would be no motivation for one skilled in the art to combine the teachings of Collen and Wu with that of Trese to obtain the claimed

invention. Accordingly, Applicants submit that combining Trese with Wu and Collen amounts to simply taking the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability, which is the essence of improper hindsight reasoning.

Applicants note that at the time the instant application was filed it was well known that plasmin consists of two polypeptide chains connected by disulfide bridges. The two chain plasmin molecule is formed from its proenzyme, plasminogen, a single-chain molecule, by limited proteolysis at two different sites on the polypeptide chain: the N-terminal A-chain (heavy chain) contains five kringle domains while the C-terminal B-chain (light chain) contains the catalytic serine protease domain. Microplasmin, unlike plasmin, lacks the five kringle domains but contains the catalytic serine protease domain.

It was well known, at the time the instant application was filed[1] that the kringle domains of plasminogen and plasmin were involved in interaction with substrate proteins (*see, e.g.*, **Appendix A**, Wiman and Wallen, "The specific interaction between plasminogen and fibrin: A physiological role of the lysine binding site in plasminogen," *Thrombosis Research*, **1**:213-222 (especially page 219); and **Appendix A**, Wiman and Collen, "Molecular Mechanism of physiological fibrinolysis," *Nature* 272(6):549-550 (especially page 550, left column, first full paragraph)). The kringles of plasmin were known to bind zwitterionic carboxy-terminal lysine residues and lysine analogues (*e.g.*, 6-aminohexanoic acid), and this was known to be the basis for plasmin's interactions with several proteins including, but not limited to, fibrin, antiplasmin, histidine-rich glycoprotein, and tetranectin. It was further well-known in the art that for an enzyme to function effectively it would need to interact with its substrate(s).

Given the importance of the kringle domains of plasmin in substrate interactions, and the absence of these domains in microplasmin, Applicants respectfully aver that one of ordinary skill in the art would not have been motivated to replace plasmin in the methods of Trese with the microplasmin of Collen and Wu. In fact, the references cited above and the knowledge available to one of ordinary skill in the art would teach away from such a combination because,

[1] This information was also known at the time that Trese's application was filed evidencing that one of ordinary skill in the art would not think of microplasmin as a substitute for plasmin.

in the absence of substrate binding, the ability of the enzyme to function as required would be expected to impact negatively.

Furthermore, there would simply have been no reasonable expectation of success in using microplasmin in the eye. Nor would Collen and Wu have suggested any expectation of success. As stated above, neither reference teaches or suggests treatment of or administration to the eye. The treatment of stroke as disclosed in Collen and Wu would not provide any expectation of success for using microplasmin in the method taught in Trese. Trese's own work suggests that it was not obvious to combine the art as proposed in the Office Action (*see,* U.S. Patent No. 5,304,118 and U.S. Patent Application Publication No. 20060024349, filed after the publication of Wu and Collen, respectively). This strongly suggests that replacing plasmin with microplasmin for use in the eye would not have been obvious to one of skill in the art.

For the foregoing reasons, Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

(b) Claims 57, 63, 66, and 70 were rejected 35 U.S.C. § 103(a) as purportedly being unpatentable over Trese *et al.* (U.S. Patent No. 5,304,118) in view of Collen *et al.* (WO 2002/50290) in further view of Wu *et al.* (U.S. Patent No. 4,774,087) and Tanaka *et al.* (*see,* Office action, page 7).

For the reasons discussed above, the combination of Trese, Collen and Wu do not render obvious Applicants' claimed invention. Nor would there have been any motivation to combine the references as proposed, as also set forth above. Tanaka does not remedy this deficiency. In fact, Tanaka further bolsters the non-obviousness of using microplasmin. Tanaka's article, published in 2000, describes studies relating to enzyme-assisted vitrectomy. Although Tanaka's article was published well after the description of microplasmin in the cited Wu reference, Tanaka does not suggest, or even hint at, using microplasmin as an alternative to plasmin in pharmacological vitrectomy. This further evidences the non-obviousness of using microplasmin as claimed by Applicants.

Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

Claims 57-84 remain pending in the instant application. Claims 57-61, 63-72, and 80-84 are under examination in the instant application. As set forth above, these claims are believed to be in condition for allowance. Further and favorable action in the form of a Notice of Allowance is respectfully requested.

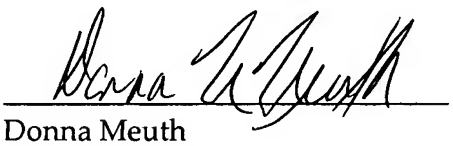
Other than the fees related to the Supplemental Information Disclosure Statement, no additional fees are believed to be due in connection with this filing. However, if any fees are due, please charge the requisite fees to Deposit Account No. 08-0219.

If the Examiner has any questions relating to this application, he is invited to call the undersigned at the telephone number indicated below.

Respectfully submitted,

WILMER CUTLER PICKERING HALE AND DORR LLP

Date: July 25, 2007



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APPENDIX A

Attached is a copy of a Supplemental Information Disclosure Statement.